

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460



OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: June 22, 2020

SUBJECT: Dicamba: Absorption, distribution, depletion, and excretion of [phenyl-U-¹⁴C] in SAN 837 H in the rat

PC Code: 029801
Decision Nos.: 563960
Petition No.: N/A
Risk Assessment Type: N/A
TXR No: 0058053
MRID Nos.: 51136001

DP Barcodes: D458237
Registration No.: 100-1623
Regulatory Action: N/A
Case No.: N/A
CAS No.: 1918-00-9
40 CFR: N/A

FROM: Sarah Dobreniecki Ph.D., Biologist
Risk Assessment Branch VII
Health Effects Division, 7509P

A handwritten signature in cursive script, appearing to read "Sarah Dobreniecki".

THROUGH: Michael Metzger, Branch Chief
Risk Assessment Branch V/VII
Health Effects Division, 7509P

A handwritten signature in cursive script, appearing to read "Michael Metzger".

TO: Margaret Hathaway, Risk Manager Reviewer
Reuben Baris, Risk Manager (PY1 S-7227)
Registration Division (7505P)

I. CONCLUSIONS

The study titled, "Dicamba: Absorption, distribution, depletion, and excretion of [phenyl-U-¹⁴C] in SAN 837 H in the rat" (MRID 51136001) was reviewed.

This study is classified **acceptable/guideline** and satisfies the guideline requirements for a metabolism study (OCSPP 870.7485; OECD 417) in rats.

II. ACTION REQUESTED

The Registration Division (RD) of the Office of Pesticide Programs (OPP) requested that the Health Effects Division (HED) review and create a Data Evaluation Record (DER) for the data submitted by the Dicamba Task Force.

III. RESULTS/DISCUSSION

Hassler, S. (2002). Dicamba: Absorption, distribution, depletion, and excretion of [phenyl-U-¹⁴C] in SAN 837 H in the rat. Syngenta Crop Protection AG, Basel, Switzerland. Laboratory Project ID: 050AM01, September 5, 2002. MRID 51136001. Unpublished.

EXECUTIVE SUMMARY: In a mass balance/excretion/pharmacokinetics/tissue distribution study (MRID 51136001), [phenyl-U-ring-¹⁴C]-dicamba (Batch # ILA-72.1; radiochemical purity 99.2% and 99.4%) was investigated after nominal single oral gavage doses of 0.5 or 200 mg/kg to Han Wistar rats (n = 4/sex/dose level or n = 3/sex/time point/dose level).

No unusual behavior was observed in any treatment group prior to or after dose administration.

Mean blood concentrations at each time point were generally similar between males and females at each dose level although occasional differences of approximately ≤ 2 -fold occurred. Serial blood concentrations after administration of 0.5 mg/kg [¹⁴C]-dicamba to male and female rats were quantifiable through 8 h and 12 h post-dose, respectively, and concentrations after administration of 200 mg/kg [¹⁴C]-dicamba were quantifiable through 48 h post-dose in both sexes.

After administration of 0.5 mg/kg [¹⁴C]-dicamba to male and female rats, the C_{max} of radioactive residues in whole blood was 0.11 and 0.13 µg-equiv/g, respectively, at 0.5 h (T_{Cmax1}). A second maximum in males and females of 0.05 and 0.08 µg-equiv/g, respectively, was reached at 2 and 4 h (T_{Cmax2}) and blood concentrations declined from the secondary peaks by half within 3-5 h (7 h post-dose). After administration of 200 mg/kg to male and female rats, the C_{max} of radioactive residues in whole blood was 67.6 and 50.5 µg-equiv/g, respectively, at 0.5 h (T_{Cmax1}). A second maximum in males and females of 32.9 and 30.7 µg-equiv/g, respectively, also was reached at 4 h (T_{Cmax2}) and blood concentrations declined from the secondary peaks by half within 3-6 h (7-10 h post-dose).

Estimates of AUC_{0-t} in the 0.5 mg/kg males and females were 0.37 and 0.58 µg-equiv × h/g, respectively. Estimates of AUC_{0-t} in the 200 mg/kg males and females were 273 and 315 µg-equiv × h/g, respectively. Estimates of AUC_{0-t} for females were greater compared to males and this difference was more evident after administration of 0.5 mg/kg with an increase of approximately 60% in females compared to males. At the high dose, the estimated AUC_{0-t} values increased in both sexes in a non-proportional manner with increases of approximately 742-fold for males and 541-fold for females for the 400-fold dose ratio.

Oral administration of 0.5 or 200 mg/kg [¹⁴C]-dicamba resulted in nearly complete absorption from the gastrointestinal tract into the systemic circulation. Estimated oral bioavailability was

generally >90% of the administered dose independent of dose level and sex. The percentages and rates of excretion in urine and feces through 168 h generally were similar between males and females regardless of dose level. Recovery of radioactive residues in urine was rapid with >95% and approximately 85% excreted in males and females, respectively, at 0.5 mg/kg and >95% excreted in both sexes at 200 mg/kg. Recovery of radioactive residues in feces was minor with approximately 1-2% of the administered dose recovered. Less than 0.01% of the administered radioactivity was detected in the expired-air traps through 48 h post-dose in the 200 mg/kg dose group. Similarly, recoveries of radioactive residues in excise tissues/organs at 168 h post-dose were <0.1% of the administered doses. The percentage of radioactive residues remaining in the residual carcasses at 168 h post-dose administration was <0.1% in the 0.5 mg/kg males and <0.2% in the 0.5 mg/kg females and the 200 mg/kg rats. Total recoveries after administration of the 0.5 mg/kg dose were approximately 92-99% with approximately 98-100% recovered after administration of the 200 mg/kg dose.

The radioactive residue levels in all selected tissues and organs were greatest at 4 h post-dose which generally corresponded to the second blood maximum concentration. The tissue elimination half-life estimates generally were 2 h for the 0.5 mg/kg treatment group and 2 or 3 h for the 200 mg/kg treatment group illustrating the rapid tissue clearance at both dose levels.

At 0.5 mg/kg, the greatest tissue concentrations were observed in kidneys (0.20 and 0.33 µg-equiv/g), with further concentrations of ≥ 0.05 µg-equiv/g in plasma and blood for males and females as well as the lungs, ovaries, and uterus in females. The maximum radioactive residue concentrations in all other tissues were <0.05 µg-equiv/g. Maximum tissue radioactive residue concentrations were up to 2-fold greater in females compared to males. Tissue concentrations were close to or less than the lower limits of quantification or detection within 16 h post-dose.

At 200 mg/kg, the greatest tissue concentrations in males and females were observed in kidneys (86.9 and 68.6 µg-equiv/g, respectively), plasma (34.9 and 39.6 µg-equiv/g, respectively), and blood (21.0 and 23.3 µg-equiv/g, respectively) with further concentrations between 10-20 µg-equiv/g in adrenals, heart, liver, and lungs as well as the thyroids, ovaries, and uterus in females. The maximum radioactive residue concentrations in all other tissues were <10.0 µg-equiv/g. Maximum tissues radioactive residue concentrations generally were similar in females compared to males. Tissue concentrations generally were greater than the limits of quantification through 16 h post-dose.

Tissue concentrations of radioactive residues at 168 h post-dose at 0.5 mg/kg were at or less than the lower limits of quantification. Tissue concentrations of radioactive residues at 168 h post-dose at 200 mg/kg were quantifiable (0.01-0.03 µg-equiv/g) in the kidneys, plasma, liver, and lungs in males and females as well as the blood, muscle, pancreas, spleen, and uterus in females. All other tissue concentrations were at or less than the lower limits of quantification. Radioactive residues in the residual carcasses at 168 h post-dose were at or less than the lower limits of quantification in the 0.5 mg/kg dose group and 0.3-0.4 µg-equiv/g in the 200 mg/kg dose group.

This study is classified **acceptable/guideline** and satisfies the guideline requirements for a metabolism study (OCSPP 870.7485; OECD 417) in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. It was stated that the study was conducted in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26, 1997 by decision of the OECD Council [C(97)186/Final].

DATA EVALUATION RECORD

DICAMBA (SAN 837 H)

Study Type: OCSP 870.7485; Metabolism and Pharmacokinetics

EPA Contract No. EP-W-16-018

Task Assignment No. 33-2-029 (MRID 51136001)

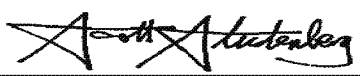
Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by

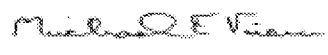


10560 Arrowhead Dr., Suite 500
Fairfax, VA 22030


Primary Reviewer:
Scott D. Studenberg, Ph.D., DABT

Signature: 
Date: 05/19/2020

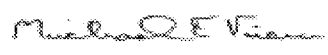
Secondary Reviewer:
Michael E. Viana, Ph.D.

Signature: 
Date: 06/05/2020

Quality Assurance:
Sarah E. Saucier, Ph.D.

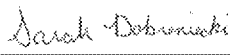
Signature: 
Date: 06/09/2020

Project Manager:
Michael E. Viana, Ph.D.

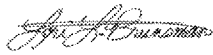
Signature: 
Date: 06/10/2020

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by CDM/CSS-Dynamac Joint Venture personnel. Contractor's role did not include establishing Agency policy.

EPA Reviewer: Sarah Dobreniecki
Risk Assessment Branch VII, HED (7509P)

Signature: 
Date: 06/22/2020

EPA Contract Officer Representative: Lori Brunzman
Science Information Mgmt. Branch, HED (7509P)

Signature: 
Date: 06/22/2020
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Metabolism and Pharmacokinetics - Rat; OCSPP 870.7485 [§85-1];
OECD 417.

PC CODE: 029801

DP BARCODE: D458237

TXR#: 0058053

TEST MATERIALS (PURITY): [Phenyl-U-¹⁴C]-Dicamba; 99.2% and 99.4%)

SYNONYMS: SAN 837 H, 3,6-dichloro-2-methoxybenzoic acid

CITATIONS: Hassler, S. (2002). Dicamba: Absorption, distribution, depletion, and excretion of [phenyl-U-¹⁴C] in SAN 837 H in the rat. Syngenta Crop Protection AG, Basel, Switzerland. Laboratory Project ID: 050AM01, September 5, 2002. MRID 51136001. Unpublished.

SPONSOR: Syngenta Crop Protection AG, Basel, Switzerland

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A second maximum in males and females of 32.9 and 30.7 µg-equiv/g, respectively, also was reached at 4 h ($T_{C_{max2}}$) and blood concentrations declined from the secondary peaks by half within 3-6 h (7-10 h post-dose).

Estimates of AUC_{0-t} in the 0.5 mg/kg males and females were 0.37 and 0.58 µg-equiv × h/g, respectively. Estimates of AUC_{0-t} in the 200 mg/kg males and females were 273 and 315 µg-equiv × h/g, respectively. Estimates of AUC_{0-t} for females were greater compared to males and this difference was more evident after administration of 0.5 mg/kg with an increase of approximately 60% in females compared to males. At the high dose, the estimated AUC_{0-t} values increased in both sexes in a non-proportional manner with increases of approximately 742-fold for males and 541-fold for females for the 400-fold dose ratio.

Oral administration of 0.5 or 200 mg/kg [^{14}C]-dicamba resulted in nearly complete absorption from the gastrointestinal tract into the systemic circulation. Estimated oral bioavailability was generally >90% of the administered dose independent of dose level and sex. The percentages and rates of excretion in urine and feces through 168 h generally were similar between males and females regardless of dose level. Recovery of radioactive residues in urine was rapid with >95% and approximately 85% excreted in males and females, respectively, at 0.5 mg/kg and >95% excreted in both sexes at 200 mg/kg. Recovery of radioactive residues in feces was minor with approximately 1-2% of the administered dose recovered. Less than 0.01% of the administered radioactivity was detected in the expired-air traps through 48 h post-dose in the 200 mg/kg dose group. Similarly, recoveries of radioactive residues in excise tissues/organs at 168 h post-dose were <0.1% of the administered doses. The percentage of radioactive residues remaining in the residual carcasses at 168 h post-dose administration was <0.1% in the 0.5 mg/kg males and <0.2% in the 0.5 mg/kg females and the 200 mg/kg rats. Total recoveries after administration of the 0.5 mg/kg dose were approximately 92-99% with approximately 98-100% recovered after administration of the 200 mg/kg dose.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test compounds:

Radiolabeled test compound:

Radiochemical purity:

Specific activity:

Batch #:

Expiration/storage:

Structure:

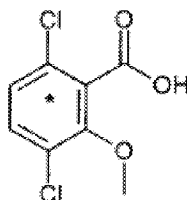
[Phenyl-U-¹⁴C]-dicamba

99.4% and 99.2%

2930 kBq/mg (79.2 µCi/mg)

ILA-72.1 (two separate batches)

November 30, 2000 and January 31, 2001/Storage conditions were not provided



* indicates position of ¹⁴C-label

Non-Radiolabeled TGAI:

Description:

Batch #:

Purity:

CAS # of TGAI:

Expiration/storage:

Structure:

Dicamba (SAN 837 H)

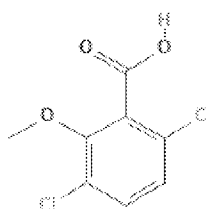
Not provided

AMS 163/101

>99.6%

1918-00-9

June 2001/Storage conditions were not provided



2. Vehicle: Polyethylene glycol 200:ethanol:water, 5:3:2 (v:v:v)

3. Test animals:

Species:

Strain:

Age/weight at administration:

Source:

Housing:

Diet:

Water:

Environmental conditions:

Acclimation period:

Rat

Han Wistar [Hanlbm: WIST (SPF)]

7 weeks (male) and 11 weeks (female, nulliparous and non-pregnant)

184-226 g (male)/172-210 g (female)

RCC Biotechnology & Animal Breeding Division (Füllinsdorf, Switzerland)

Group-housed in polycarbonate cages during acclimation and housed individually in open plexiglass metabolism cages, except for Group D1 that were housed individually in closed glass metabolism cages.

Certified diet, Nafag No. 890 (Nafag, Gossau, Switzerland), *ad libitum*.

Tap water, *ad libitum*.

Temperature: 20-22°C

Humidity: 48-86%

Air changes: Not provided

Photoperiod: 12 h light:12 h dark

≥5 days

4. Preparation of dosing solutions: It was stated that the test substance was dissolved in a mixture of polyethylene glycol 200:ethanol:water, 5:3:2 (v:v:v) at concentrations of about

0.1 and 40 mg/mL for the low- and high-dose levels, respectively. For the high-dose formulations, [^{14}C]-dicamba was diluted with unlabeled dicamba to achieve specific activities of 271 kBq/mg (7.3 $\mu\text{Ci}/\text{mg}$; Group D1) and 96 kBq/mg (2.6 $\mu\text{Ci}/\text{mg}$; Groups F3/F4). No further details regarding dose formulation preparation were provided.

Each dose formulation concentration was determined by transferring a 1-mL portion of the formulation (control dose) into a volumetric flask. Dilution details were not provided. Radioactivity was determined in triplicate for each control dose by liquid scintillation counting (LSC) and the respective dose was calculated. Three to four control dose evaluations were conducted for each dose formulation. The results of these concentration checks were not provided; actual dose concentration data are included below. The high-dose concentrations were acceptable (generally within $\pm 10\%$ of nominal); low-dose concentrations ranged up to 136% of nominal. Homogeneity assessments of the dose formulations also were not provided. The radiochemical purity of the test substance in the dose formulations at administration was assessed by thin-layer chromatography (TLC) at the time of dosing for each dose group by using solvent systems CI-1 and CI-2. Plate specifications and solvent systems were presented on page 28 of MRID 51136001 and are included as Appendix I at the end of the DER.

Results

Homogeneity (% RSD): Not provided

Stability (% of time 0): Not provided; acceptable based on radiochemical purity (98.1-99.4%)

Concentration (% nominal): 102-136% (low dose); 88.6-108.2% (high dose)

B. STUDY DESIGN AND METHODS

- 1. Group arrangements:** Study details are presented in Table 1. Group assignment details were not provided.

Initiation of treatment began on August 14, 2000 and the in-life portion was completed on October 25, 2000.

TABLE 1. Excretion-balance and tissue distribution study after administration of [phenyl-U-¹⁴C]-dicamba by single oral gavage administration of 0.5 or 200 mg/kg to rats. ^a

Group	Number	Radioactivity (kBq/kg) ^{b, c}	Experiment	Radiolabel dose (mg/kg)		Sample Collection
				Nominal	Actual ^c	
B1	4 males	1561 ± 96.7	Excretion/mass balance, pharmacokinetics, and tissue distribution	0.5	0.53 ± 0.03	Urine (0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 h), feces (0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 h), cage washes, blood (0.5, 1, 2, 4, 8, 12, 24, 48 h), tissues, and residual carcass
	4 females	1608 ± 54.7			0.55 ± 0.02	
D1	4 males	53954 ± 3176	Excretion/mass balance, pharmacokinetics, and tissue distribution	200	199.1 ± 11.7	Expired air (0-24 and 24-48 h), Urine (0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 h), feces (0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 h), cage washes, blood (0.5, 1, 2, 4, 8, 12, 24, 48 h), tissues, and residual carcass
	4 females	54557 ± 2011			201.3 ± 7.4	
F1	12 males	1655 ± 70.1	Tissue distribution	0.5	0.57 ± 0.03 ^b	Adrenals, bone/marrow, brain, fat, heart, kidneys, liver, lungs, muscle, ovaries, pancreas, spleen, testes, thymus, thyroids, uterus, whole blood/plasma, and residual carcass were collected from 3 rats/sex at 4, 8, 12, or 16 h
F2	12 females	1755 ± 84.8			0.60 ± 0.03 ^b	
F3	12 males	17603 ± 443	Tissue distribution	200	183.4 ± 3.56 ^b	Adrenals, bone/marrow, brain, fat, heart, kidneys, liver, lungs, muscle, ovaries, pancreas, spleen, testes, thymus, thyroids, uterus, whole blood/plasma, and residual carcass were collected from 3 rats/sex at 4, 8, 12, or 16 h
F4	12 females	19493 ± 519			203.1 ± 4.27 ^b	

^a Data were obtained from pages 23-25 and Tables 1-6 on pages 42-47 of MRID 51136001.

^b Calculated by the Reviewers.

^c Mean ± SD.

2. Dosing and sample collection

- a. Dose selection and routes:** The low dose (0.5 mg/kg) was expected to be a no-effect level and the high dose (200 mg/kg) was expected to cause toxicity based on previous studies (not specified).
- b. Dosing:** The dose solutions were administered by oral gavage at a volume of 1 mL. The mean (± SD) concentration and radioactivity values of the administered doses are shown in Table 1. After dose administration, rats were housed individually in metabolism cages until euthanasia (up to 168 h post-dose). Rats in Group D1 (expired-air collections) were housed in closed glass metabolism cages. A representative diagram of the system was shown in Figure 1 on page 80 of MRID 51136001 and is included as Appendix II at the end of the DER. Rats in Groups B1 and F1-F4 were housed in open plexiglass metabolism cages. A representative diagram of the system was shown in Figure 2 on page 82 of MRID 51136001 and is included as Appendix III at the end of the DER.

c. Sample collection

- i. **Urine:** Urine samples were collected from each rat in Groups B1 and D1 (excretion/mass balance) at 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h post-dose. Urine samples were collected in containers surrounded by solid CO₂. At each sample collection time, the funnel of each cage was washed with 5-10 mL of water and the wash was combined with the urine collection. Samples were stored frozen at $\leq -18^{\circ}\text{C}$.
- ii. **Feces:** Feces samples were collected from each rat in Groups B1 and D1 (excretion/mass balance) at 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h post-dose. Feces samples were collected at room temperature. Samples were stored frozen at $\leq -18^{\circ}\text{C}$.
- iii. **Cage washes:** Cages washes for Groups B1 and D1 were described above (B.2.c.i.). For Groups F1-4 (tissue distribution), each cage was rinsed thoroughly with water/ethanol (approximately 1:1, v:v) at the end of each collection period (i.e., 4, 8, 12, or 16 h post-dose). Samples were stored at room temperature.
- iv. **Serial blood samples:** Serial blood samples for determination of the radioactive residue concentrations were collected by cutting the tip of the tail (*vena sacralis media*). Serial blood samples were collected at 0.5, 1, 2, 4, 8, 12, 24, and 48 h post-dose.
- v. **Expired air:** Expired air samples were collected from the Group D1 rats only (200 mg/kg). Expired air was continuously pulled through the cages and exhaled CO₂ was absorbed in a mixture of ethanol amine:ethylene glycol monomethyl ether (1:2, v:v). Expired air samples were collected for the 0-24 and 24-48 h periods only. Samples were stored at room temperature.
- vi. **Organs/tissues/carcasses:** For Groups B1 and D1, rats were euthanized by exsanguination after CO₂ anesthesia at 168 h post-dose. For Groups F1-F4, three rats/time point were euthanized by exsanguination after CO₂ anesthesia at 4, 8, 12, or 16 h post-dose. Terminal blood samples were collected in heparin, portions of whole blood were taken, and plasma was harvested from the remaining blood samples by centrifugation. After euthanasia, the following tissues/organs were collected:

Adrenals	Bone (w/marrow)	Brain	Fat, abdominal	Heart	Kidneys	Liver
Lungs	Muscle (skeletal)	Ovaries (F)	Pancreas	Plasma	Spleen	Testis (M)
Thymus	Thyroids	Uterus (F)	Whole blood	Carcass		

Samples (except whole blood) were stored frozen at $\leq -18^{\circ}\text{C}$. Whole blood samples were stored refrigerated.

3. Sample treatment: Volumes and weights of biological samples were determined as appropriate.

- a. **Urine:** Portions of urine samples (0.025-1 mL) were added directly to scintillation liquid for radioanalysis by LSC.

- b. **Feces:** Each fecal sample was homogenized manually with a pestle after addition of water (volume or ratio not provided). Duplicate portions (approximately 0.2-0.32 g) of each homogenate were combusted prior to radioanalysis by LSC.
- c. **Cage washes:** Portions of cage wash collections (1 mL) were added directly to scintillation liquid for radioanalysis by LSC.
- d. **Blood/plasma:** Portions of the serial blood samples (approximately 0.11-0.73 g) or terminal blood samples (approximately 0.24-0.32 g) were combusted prior to radioanalysis by LSC. Portions of plasma samples (0.18-0.27 g) were added directly to scintillation liquid for radioanalysis by LSC.
- e. **Expired air:** Portions (2 mL) of the trapping solutions were each combined with 6-mL portions of methanol and added to scintillation liquid for radioanalysis by LSC.
- f. **Organs/tissues/carcasses:** The two adrenal glands were combined to form one specimen that was analyzed. Bone, including bone marrow, was broken into small pieces with a pair of scissors, three to four pieces were combined to produce a sample, and duplicate portions were analyzed. The brains and lungs were minced with scissors and duplicate portions of each organ were analyzed. Each ovary was one sample and both ovary samples were analyzed. Each pair of thyroids was combined to produce a single specimen that was analyzed. For the remaining tissue specimens, two to three samples from the uterus (or three to four samples for all other tissues) were combined to produce a single specimen. Duplicate portions of each were analyzed. Each residual carcass was homogenized with a chopper after addition of solid CO₂. Duplicate portions were analyzed.

The bone (0.10-0.24 g), lungs (0.20-0.28 g), and residual carcass homogenates (0.20-0.31 g) were combusted prior to radioanalysis by LSC. All remaining tissue samples were solubilized by combination with 4 mL of Soluene-350 tissue solubilizer, neutralization with 4 mL of 1 N HCl, and addition to scintillation liquid for radioanalysis by LSC.

4. **Analytical methodology**

- a. **Combustion analyses:** Selected solid samples (*i.e.*, feces homogenates, carcass, bone, lungs, serial and terminal blood samples) were combusted with a sample oxidizer. The resulting ¹⁴CO₂ was trapped in Carbosorb[®] (Packard Instrument Company, Inc., Meriden, CT), mixed with scintillation cocktail, and analyzed by LSC. Recovery tests were conducted by combusting standards of SPEC-CHEC[™]-[¹⁴C] (blend of *n*-amyl alcohol, 1,3-butandiol, and [¹⁴C]-stearic acid) at the beginning of each day and with each combustion sequence. Combustion and trapping efficiencies were >95% and all reported data were uncorrected.
- b. **Liquid scintillation counting (LSC):** Radioactivity was measured with a liquid scintillation counter equipped for computing quench-corrected disintegrations per min (dpm). Background values were determined with each run sequence against the respective scintillation liquid blank.

- c. **Thin-layer chromatography (TLC):** Thin-layer chromatography was conducted on precoated plates of silica gel SI 60 F₂₅₄ and reversed-phase RP 18 F₂₅₄, 200 × 200 mm, 0.25-mm thick. The plates were developed without chamber saturation. As noted in Section I.A.4., TLC was used to determine stability of [¹⁴C]-dicamba in the dose formulations and the solvent systems are included in Appendix I. It was noted that the chromatographic behavior of [¹⁴C]-dicamba on the reversed-phase plates was influenced by the polyethylene glycol 200 in the formulation vehicle.
5. **Statistics:** Statistical analyses were not conducted. Individual data were reported along with mean ± standard deviation (SD).

Pharmacokinetic analyses were conducted with standard equations assuming first-order kinetics. The area under the curve (AUC) estimates were calculated according to the trapezoidal method (Groups B1 and D1). The elimination (depletion) half-life of radioactive residues from each selected organ/tissue (including whole blood and plasma) was determined from the tissue distribution data (Groups F1-F4).

II. RESULTS

A. RADIOLABELED DOSE

1. **Radiochemical purity:** The radiochemical purity of formulated [¹⁴C]-dicamba (as assessed by TLC) at administration was 98.1-99.4%.
2. **Dose levels:** The mean actual doses administered are shown in Table 1. No details regarding concentration assessment of the formulations prior to or after dose administration were provided.
- B. **CLINICAL SIGNS:** It was stated that no unusual behavior was observed in any treatment group prior to or after dose administration. Some females in Groups B1 and D1 (2/4 per group) had body weight decreases of up to 4% during the seven-day post-dose period. Approximately 50% of the rats in Groups F1-F4 had body weight decreases of up to 5% prior to euthanasia at up to 16 h post-dose. These minimal decreases were considered unrelated to treatment.

C. BLOOD CONCENTRATION/PHARMACOKINETICS

1. **Concentration-time profiles:** Mean concentrations of total radioactive residues in serial whole blood samples after single oral gavage doses of [¹⁴C]-dicamba at 0.5 or 200 mg/kg (Groups B1 and D1, respectively) are provided in Table 2. Mean blood concentrations at each time point were generally similar between males and females at each dose level although occasional differences of approximately ≤2-fold occurred. Serial blood concentrations after administration of 0.5 mg/kg [¹⁴C]-dicamba to male and female rats were quantifiable through 8 h and 12 h post-dose, respectively. Blood concentrations after administration of 200 mg/kg [¹⁴C]-dicamba were quantifiable through 48 h post-dose in both sexes.

TABLE 2. Mean (\pm SD) concentrations of total radioactive residues in whole blood after a single oral dose of [phenyl- ^{14}C]-dicamba at 0.5 or 200 mg/kg to rats. ^a				
Time post-dose (h)	Concentration ($\mu\text{g-equiv/g}$)			
	0.5 mg/kg		200 mg/kg	
	Male	Female	Male	Female
0.5	0.1055 \pm 0.0366	0.1315 \pm 0.0346	67.56 \pm 41.39	50.51 \pm 14.76
1	0.0393 \pm 0.0093	0.0724 \pm 0.0264	40.27 \pm 45.89	23.16 \pm 5.608
2	0.0494 \pm 0.0243	0.0732 \pm 0.0222	25.79 \pm 5.913	22.32 \pm 2.442
4	0.0457 \pm 0.0094	0.0770 \pm 0.0200	32.86 \pm 4.377	30.69 \pm 9.456
8	0.0153 \pm 0.0130	0.0208 \pm 0.0058	11.34 \pm 4.037	23.79 \pm 9.415
12	LLOQ ^b	0.0039 \pm 0.0013	2.070 \pm 1.256	4.838 \pm 3.553
24	LLOD	LD	0.4448 \pm 0.1394	0.6513 \pm 0.4707
48	LD	LD	0.1565 \pm 0.0530	0.1283 \pm 0.0367

a Data were obtained from Tables 7-10 on pages 48-51 of MRID 51136001; n = 4 samples/time point/sex/dose level. Standard deviation values were calculated by the Reviewers.

b LLOQ = 0.0028 $\mu\text{g-equiv/g}$.

LLOQ Lower limit of quantification.

LLOD Lower limit of detection

2. **Pharmacokinetic parameters:** Estimates of pharmacokinetic parameters for whole blood after single oral gavage doses of [^{14}C]-dicamba at 0.5 or 200 mg/kg (Groups B1 and D1, respectively) are provided in Table 3.

After administration of 0.5 mg/kg [^{14}C]-dicamba to male and female rats, the C_{max} of radioactive residues in whole blood was 0.11 and 0.13 $\mu\text{g-equiv/g}$, respectively at 0.5 h (T_{Cmax1}). A second maximum in males and females of 0.05 and 0.08 $\mu\text{g-equiv/g}$, respectively, was reached at 2 and 4 h (T_{Cmax2}). Blood concentrations declined from the secondary peaks by half within 3-5 h (7 h post-dose). Estimates of AUC_{0-t} in males and females were 0.37 and 0.58 $\mu\text{g-equiv} \times \text{h/g}$, respectively.

After administration of 200 mg/kg [^{14}C]-dicamba to male and female rats, the C_{max} of radioactive residues in whole blood was 67.6 and 50.5 $\mu\text{g-equiv/g}$, respectively, at 0.5 h (T_{Cmax1}). A second maximum in males and females of 32.9 and 30.7 $\mu\text{g-equiv/g}$, respectively, was reached at 4 h (T_{Cmax2}). Blood concentrations declined from the secondary peaks by half within 3-6 h (7-10 h post-dose). Estimates of AUC_{0-t} in males and females were 273 and 315 $\mu\text{g-equiv} \times \text{h/g}$, respectively.

Estimates of AUC_{0-t} for females were greater compared to males. This difference was more evident after administration of the low dose (0.5 mg/kg) with an increase of approximately 60% in females compared to males (0.58 $\mu\text{g-equiv} \times \text{h/g}$ females vs. 0.37 $\mu\text{g-equiv} \times \text{h/g}$ males). At the high dose, the estimated AUC_{0-t} values increased in both sexes in a non-proportional manner. For the 400-fold dose ratio, the increases in AUC_{0-t} estimates were approximately 742-fold for males and 541-fold for females.

TABLE 3. Mean estimates (\pm SD) of pharmacokinetic parameters for radioactive residues in whole blood after a single oral dose of [phenyl- ^{14}C]-dicamba at 0.5 or 200 mg/kg to rats. ^a

Parameter	0.5 mg/kg		200 mg/kg	
	Male	Female	Male	Female
$C_{\max 1}$ ($\mu\text{g-equiv/g}$) ^b	0.1055 \pm 0.0366	0.1315 \pm 0.0346	67.56 \pm 41.39	50.51 \pm 14.76
$C_{\max 2}$ ($\mu\text{g-equiv/g}$) ^b	0.0494 \pm 0.0243	0.0770 \pm 0.0200	32.86 \pm 4.377	30.69 \pm 9.457
$T_{C_{\max 1}}$ (h)	0.5	0.5	0.5	0.5
$T_{C_{\max 2}}$ (h)	2	4	4	4
$T_{C_{\max 2/2}}$ (h) ^c	7	7	7	10
AUC_{0-t} ($\mu\text{g-equiv} \times \text{h/g}$)	0.3679 \pm 0.0748	0.5828 \pm 0.0651	273.1 \pm 45.4	315.1 \pm 87.4

a Data were obtained from page 33 and Tables 7-10 on pages 48-51 of MRID 51136001; n = 4 samples/time point/sex/dose level.

b Mean (\pm SD) copied from Table 2 above.

c Time for the blood concentration at $T_{C_{\max 2}}$ to be reduced by half.

D. MASS BALANCE AND EXCRETION: The cumulative mean (\pm SD) percentage recoveries of the dose after single oral gavage doses of [^{14}C]-dicamba at 0.5 or 200 mg/kg (Groups B1 and D1, respectively) are provided in Table 4.

Oral administration of 0.5 or 200 mg/kg [^{14}C]-dicamba resulted in nearly complete absorption from the gastrointestinal tract into the systemic circulation. Oral bioavailability (estimated as the sum of radioactive residues recovered in urine, expired air, and tissue/carcass) was calculated as generally >90% of the administered dose independent of dose level and sex. Although the estimated bioavailability for females at the 0.5 mg/kg level was only 87.4% of the dose, the percentage of radioactive residues in the cage wash (considered as dried urine) accounted for an additional 3.1% of the dose.

The percentages and rates of excretion in urine and feces through 168 h generally were similar between males and females and regardless of dose level. Recovery of radioactive residues in urine was rapid with >95% and approximately 85% excreted in males and females, respectively, at 0.5 mg/kg and >95% excreted in both sexes at 200 mg/kg. Recovery of radioactive residues in feces was minor with <1% of the administered dose recovered, except for a recovery of <2% in the 0.5 mg/kg females. Less than 0.01% of the administered radioactivity was detected in the expired-air traps through 48 h post-dose in the 200 mg/kg dose group. Similarly, recoveries of radioactive residues in excise tissues/organs at 168 h post-dose were <0.1% of the administered doses. The percentage of radioactive residues remaining in the residual carcasses at 168 h post-dose administration was <0.1% for the 0.5 mg/kg males and <0.2% for the 0.5 mg/kg females and the 200 mg/kg rats. Total recoveries after administration of the 0.5 mg/kg dose were approximately 92-99% with approximately 98-100% recovered after administration of the 200 mg/kg dose.

TABLE 4. Mean (\pm SD) excretion of radioactive residues (% of administered dose) after a single oral dose of [phenyl-U- 14 C]-dicamba at 0.5 or 200 mg/kg to rats. ^a

Matrix	Time (h)	0.5 mg/kg		200 mg/kg	
		Male	Female	Male	Female
Urine	0-6	76.21 \pm 3.21	64.57 \pm 1.00	73.17 \pm 6.60	62.25 \pm 4.19
	6-12	18.49 \pm 3.67	17.14 \pm 3.26	21.72 \pm 4.57	33.22 \pm 5.63
	12-24	1.94 \pm 0.49	2.78 \pm 0.55	1.99 \pm 0.36	2.84 \pm 0.77
	24-48	0.37 \pm 0.14	1.28 \pm 0.08	0.51 \pm 0.12	0.77 \pm 0.26
	48-72	0.19 \pm 0.11	0.59 \pm 0.15	0.11 \pm 0.02	0.18 \pm 0.07
	72-96	0.10 \pm <0.01	0.38 \pm 0.06	0.06 \pm 0.02	0.09 \pm 0.03
	96-120	0.06 \pm 0.01	0.25 \pm 0.09	0.03 \pm 0.01	0.03 \pm <0.01
	120-144	0.05 \pm 0.02	0.16 \pm 0.09	0.03 \pm 0.01	0.01 \pm <0.01
	144-168	0.03 \pm <0.01	0.09 \pm 0.03	0.03 \pm 0.02	0.02 \pm <0.01
Urine Total	0-168	97.44 \pm 2.27	87.25 \pm 3.03	97.65 \pm 2.53	99.41 \pm 2.45
Feces	0-24	0.60 \pm 0.17	1.26 \pm 0.55	0.29 \pm 0.19	0.32 \pm 0.23
	24-48	0.07 \pm 0.05	0.28 \pm 0.23	0.06 \pm 0.02	0.27 \pm 0.30
	48-72	0.02 \pm 0.01	0.05 \pm 0.02	0.02 \pm 0.01	0.03 \pm 0.02
	72-96	0.02 \pm 0.01	0.05 \pm 0.03	0.01 \pm <0.01	<0.01 \pm <0.01
	96-120	0.02 \pm 0.02	0.02 \pm <0.01	<0.01 \pm <0.01	0.04 \pm 0.07
	120-144	<0.01 \pm <0.01	0.02 \pm 0.01	<0.01 \pm <0.01	<0.01 \pm <0.01
	144-168	0.01 \pm 0.02	0.04 \pm 0.03	0.09 \pm 0.12	0.02 \pm <0.01
Feces total	0-168	0.75 \pm 0.18	1.72 \pm 0.71	0.49 \pm 0.27	0.69 \pm 0.31
Expired air	0-24	NA	NA	<0.01 \pm <0.01	<0.01 \pm <0.01
	24-48	NA	NA	<0.01 \pm <0.01	<0.01 \pm <0.01
Expired air total	0-48	NA	NA	<0.01 \pm <0.01	<0.01 \pm <0.01
Cage wash	168	0.48 \pm 0.36	3.09 \pm 1.80	0.15 \pm 0.04	0.13 \pm 0.05
Excretion total	0-168	98.67 \pm 2.18	92.05 \pm 0.98	98.29 \pm 2.64	100.24 \pm 2.72
Tissues/organs	168	<0.01 \pm <0.01	<0.01 \pm <0.01	<0.01 \pm <0.01	<0.01 \pm <0.01
Residual carcass	168	<0.01 \pm <0.01	0.15 \pm 0.14	0.14 \pm 0.02	0.17 \pm 0.12
Tissue/carcass total	168	<0.01 \pm <0.01	0.15 \pm 0.14	0.14 \pm 0.02	0.17 \pm 0.12
Systemic bioavailability ^b	0-168	97.44	87.39	97.80	99.58
Total recovery	0-168	98.67 \pm 2.18	92.20 \pm 0.91	98.43 \pm 2.64	100.4 \pm 2.74

a Data were obtained from page 33 and Tables 11-14 on pages 52-55 of MRID 51136001; n = 4 rats/sex/dose level.

b Recovery in urine, expired air, and tissue/carcass.

NA Not applicable

- D. TISSUE DISTRIBUTION:** Selected organs/tissue and the residual carcass were collected and the distribution of radioactive residues was determined at 4, 8, 12, and 16 h post-dose from three rats/sex/time point/dose level (Groups F1-F4). The mean (\pm SD) tissue concentrations of radioactive residues (μ g-equiv/g) after a single oral dose of [14 C]-dicamba at 0.5 mg/kg to male and female rats are summarized in Tables 5 and 6, respectively. The mean (\pm SD) tissue concentrations of radioactive residues (μ g-equiv/g) after a single oral dose of [14 C]-dicamba at 200 mg/kg to male and female rats are summarized in Tables 7 and 8, respectively.

The radioactive residue levels in all selected tissues and organs were greatest at 4 h post-dose which generally corresponded to the second blood maximum concentration. A table summarizing the maximum radioactive residue levels and calculated tissue elimination half-life estimates was shown on page 35 of MRID 51136001 and is included as Appendix IV at the end of the DER. The tissue elimination half-life estimates generally were 2 h for the 0.5 mg/kg treatment group (range 2-3 h) and 2 or 3 h for the 200 mg/kg treatment group (range 2-4 h) illustrating the rapid tissue clearance at both dose levels.

At the low-dose level (0.5 mg/kg), the greatest tissue concentrations in males and females were observed in kidneys (0.20 and 0.33 µg-equiv/g, respectively), plasma (0.07 and 0.15 µg-equiv/g, respectively), and blood (0.05 and 0.09 µg-equiv/g, respectively) as well as the lungs (0.06 µg-equiv/g), ovaries (0.05 µg-equiv/g), and uterus (0.06 µg-equiv/g) in females. The maximum radioactive residue concentrations in all other tissues were <0.05 µg-equiv/g. Maximum tissue radioactive residue concentrations were up to 2-fold greater in females compared to males. Tissue concentrations were close to or less than the lower limits of quantification or detection within 16 h post-dose.

At the high-dose level (200 mg/kg), the greatest tissue concentrations in males and females were observed in kidneys (86.9 and 68.6 µg-equiv/g, respectively), plasma (34.9 and 39.6 µg-equiv/g, respectively), blood (21.0 and 23.3 µg-equiv/g, respectively), adrenals (16.7 and 10.1 µg-equiv/g, respectively), heart (13.1 and 15.4 µg-equiv/g, respectively), liver (12.2 and 14.2 µg-equiv/g, respectively), and lungs (14.7 and 17.6 µg-equiv/g, respectively) as well as the thyroids (10.3 µg-equiv/g), ovaries (13.1 µg-equiv/g), and uterus (16.0 µg-equiv/g) in females. The maximum radioactive residue concentrations in all other tissues were <10.0 µg-equiv/g. Maximum tissues radioactive residue concentrations generally were similar in females compared to males. Tissue concentrations generally were greater than the limits of quantification through 16 h post-dose.

TABLE 5. Mean (± SD) concentrations of radioactive residues in tissues (µg-equiv/g) after a single oral dose of [phenyl-U- ¹⁴ C]-dicamba at 0.5 mg/kg to male rats. ^a				
Tissue/organ	Termination time (h)			
	4	8	12	16
Adrenals	0.0188 ± 0.0047	0.0080 ± 0.0051	<0.0032 ± 0.0012	<LD ± 0.0002
Blood	0.0453 ± 0.0087	0.0108 ± 0.0067	0.0012 ± 0.0004	0.0008 ± 0.0005
Bone	0.0120 ± 0.0019	0.0028 ± 0.0022	<LD ± <0.0001	LD ± <0.0001
Brain	0.0023 ± 0.0006	<0.0007 ± 0.0002	LD ± <0.0001	LD ± <0.0001
Fat	0.0050 ± 0.0011	0.0012 ± 0.0006	LD ± <0.0001	LD ± <0.0001
Heart	0.0291 ± 0.0053	0.0066 ± 0.0042	0.0009 ± 0.0002	<0.0008 ± 0.0001
Kidneys	0.2003 ± 0.0669	0.0669 ± 0.0456	0.0081 ± 0.0026	0.0051 ± 0.0007
Liver	0.0372 ± 0.0066	0.0113 ± 0.0051	0.0020 ± 0.0004	0.0011 ± 0.0003
Lungs	0.0314 ± 0.0051	0.0081 ± 0.0065	<0.0009 ± 0.0004	<LD ± 0.0002
Muscle	0.0136 ± 0.0030	0.0029 ± 0.0019	<0.0007 ± 0.0002	<0.0007 ± <0.0001
Pancreas	0.0211 ± 0.0038	0.0053 ± 0.0041	<0.0019 ± 0.0003	<LD ± 0.0001
Plasma	0.0748 ± 0.0132	0.0183 ± 0.0115	0.0030 ± 0.0006	0.0019 ± 0.0003
Spleen	0.0180 ± 0.0037	0.0040 ± 0.0025	<0.0009 ± 0.0002	<0.0009 ± <0.0001
Testes	0.0193 ± 0.0050	0.0058 ± 0.0017	0.0009 ± <0.0001	<0.0007 ± <0.0001
Thymus	0.0119 ± 0.0016	0.0027 ± 0.0017	<0.0008 ± <0.0001	LD ± <0.0001
Thyroids	0.0196 ± 0.0032	<0.0080 ± 0.0020	<LD ± 0.0006	<LD ± 0.0007

^a Data were obtained from Tables 19-22 on pages 60-63 of MRID 51136001; n = 3 rats/time point.

LD Lower limit of detection (calculated as the limit of quantification [LQ]/3).

TABLE 6. Mean (\pm SD) concentrations of radioactive residues in tissues ($\mu\text{g-equiv/g}$) after a single oral dose of [phenyl- U - ^{14}C]-dicamba at 0.5 mg/kg to female rats. ^a

Tissue/organ	Termination time (h)			
	4	8	12	16
Adrenals	0.0414 \pm 0.0122	0.0078 \pm 0.0071	<0.0021 \pm 0.0016	<LD \pm 0.0003
Blood	0.0880 \pm 0.0332	0.0164 \pm 0.0146	0.0039 \pm 0.0035	<0.0008 \pm 0.0005
Bone	0.0143 \pm 0.0031	0.0052 \pm 0.0046	0.0015 \pm 0.0011	<LD \pm 0.0002
Brain	0.0039 \pm 0.0010	0.0012 \pm 0.0007	0.0005 \pm 0.0002	<0.0005 \pm <0.0001
Fat	0.0090 \pm 0.0069	0.0016 \pm 0.0010	0.0009 \pm 0.0003	0.0005 \pm <0.0001
Heart	0.0395 \pm 0.0202	0.0096 \pm 0.0082	0.0019 \pm 0.0016	0.0005 \pm 0.0001
Kidneys	0.3288 \pm 0.2564	0.0530 \pm 0.0487	0.0155 \pm 0.0128	0.0052 \pm 0.0027
Liver	0.0396 \pm 0.0168	0.0056 \pm 0.0050	0.0018 \pm 0.0009	0.0007 \pm 0.0001
Lungs	0.0602 \pm 0.0186	0.0116 \pm 0.0101	0.0023 \pm 0.0023	LD \pm 0.0002
Muscle	0.0212 \pm 0.0095	0.0031 \pm 0.0027	0.0012 \pm 0.0009	0.0005 \pm 0.0001
Ovaries	0.0527 \pm 0.0253	0.0107 \pm 0.0077	0.0040 \pm 0.0014	<0.0022 \pm 0.0001
Pancreas	0.0369 \pm 0.0106	0.0057 \pm 0.0044	0.0044 \pm 0.0033	<0.0017 \pm 0.0009
Plasma	0.1491 \pm 0.0514	0.0294 \pm 0.0260	0.0071 \pm 0.0062	0.0013 \pm 0.0009
Spleen	0.0198 \pm 0.0063	0.0046 \pm 0.0040	0.0014 \pm 0.0008	<0.0008 \pm <0.0001
Thymus	0.0210 \pm 0.0061	0.0054 \pm 0.0042	0.0015 \pm 0.0008	0.0007 \pm <0.0001
Thyroids	0.0291 \pm 0.0078	<0.0116 \pm 0.0062	<LD \pm 0.0016	<LD \pm <0.0001
Uterus	0.0608 \pm 0.0334	0.0127 \pm 0.0109	0.0030 \pm 0.0022	0.0010 \pm 0.0003

^a Data were obtained from Tables 23-26 on pages 64-67 of MRID 51136001; n = 3 rats/time point.

LD Lower limit of detection (calculated as the limit of quantification [LQ]/3).

TABLE 7. Mean (\pm SD) concentrations of radioactive residues in tissues ($\mu\text{g-equiv/g}$) after a single oral dose of [phenyl- U - ^{14}C]-dicamba at 200 mg/kg to male rats. ^a

Tissue/organ	Termination time (h)			
	4	8	12	16
Adrenals	16.657 \pm 12.173	5.495 \pm 1.510	1.125 \pm 0.409	0.461 \pm 0.593
Blood	20.978 \pm 9.626	12.353 \pm 2.447	3.022 \pm 1.120	0.633 \pm 0.521
Bone	4.671 \pm 2.290	2.885 \pm 0.823	0.703 \pm 0.117	0.461 \pm 0.544
Brain	1.085 \pm 0.572	0.814 \pm 0.207	0.159 \pm 0.056	0.037 \pm 0.027
Fat	1.875 \pm 0.758	1.058 \pm 0.077	0.359 \pm 0.124	0.171 \pm 0.186
Heart	13.116 \pm 6.681	8.478 \pm 1.930	1.823 \pm 0.718	0.455 \pm 0.485
Kidneys	86.880 \pm 4.016	59.308 \pm 5.180	18.441 \pm 11.767	4.429 \pm 2.253
Liver	12.219 \pm 4.315	9.653 \pm 2.878	2.624 \pm 0.858	0.740 \pm 0.571
Lungs	14.653 \pm 5.514	10.785 \pm 3.836	2.105 \pm 0.859	0.499 \pm 0.387
Muscle	5.661 \pm 2.791	3.383 \pm 0.667	0.748 \pm 0.254	0.174 \pm 0.157
Pancreas	7.018 \pm 3.205	5.767 \pm 1.788	1.670 \pm 0.694	1.281 \pm 1.739
Plasma	34.945 \pm 15.397	21.330 \pm 3.950	5.279 \pm 1.729	1.120 \pm 0.863
Spleen	6.901 \pm 3.259	4.129 \pm 0.849	1.028 \pm 0.265	0.408 \pm 0.548
Testes	5.675 \pm 1.551	4.633 \pm 0.443	1.166 \pm 0.328	0.302 \pm 0.191
Thymus	4.899 \pm 2.451	3.406 \pm 0.723	0.693 \pm 0.270	0.191 \pm 0.205
Thyroids	7.431 \pm 3.310	5.366 \pm 0.352	1.102 \pm 0.571	0.373 \pm 0.386

^a Data were obtained from Tables 27-30 on pages 68-71 of MRID 51136001; n = 3 rats/time point.

TABLE 8. Mean (\pm SD) concentrations of radioactive residues in tissues ($\mu\text{g-equiv/g}$) after a single oral dose of [phenyl- $U\text{-}^{14}\text{C}$]-dicamba at 200 mg/kg to female rats. ^a

Tissue/organ	Termination time (h)			
	4	8	12	16
Adrenals	10.114 \pm 2.578	7.050 \pm 4.450	1.579 \pm 1.071	0.276 \pm 0.242
Blood	23.321 \pm 5.374	15.992 \pm 10.987	3.448 \pm 2.278	0.614 \pm 0.542
Bone	3.566 \pm 0.909	2.597 \pm 1.417	0.745 \pm 0.170	0.410 \pm 0.339
Brain	1.366 \pm 0.398	0.959 \pm 0.693	0.177 \pm 0.086	0.075 \pm 0.101
Fat	1.841 \pm 0.587	1.600 \pm 1.246	0.287 \pm 0.129	0.082 \pm 0.069
Heart	15.399 \pm 2.084	9.825 \pm 6.662	1.925 \pm 1.339	0.388 \pm 0.349
Kidneys	68.568 \pm 20.376	66.072 \pm 36.284	15.317 \pm 9.587	3.876 \pm 3.357
Liver	14.217 \pm 0.935	10.308 \pm 6.539	2.329 \pm 1.495	0.509 \pm 0.458
Lungs	17.620 \pm 1.141	11.066 \pm 6.867	2.297 \pm 1.528	0.366 \pm 0.331
Muscle	5.701 \pm 1.840	3.794 \pm 2.656	0.709 \pm 0.585	0.174 \pm 0.165
Ovaries	13.112 \pm 3.372	8.554 \pm 5.920	1.728 \pm 0.969	0.920 \pm 0.793
Pancreas	9.165 \pm 1.881	6.386 \pm 5.551	1.122 \pm 0.817	0.373 \pm 0.336
Plasma	39.567 \pm 9.159	26.520 \pm 17.898	5.976 \pm 3.786	1.045 \pm 0.937
Spleen	7.749 \pm 2.428	5.294 \pm 3.539	1.098 \pm 0.775	0.265 \pm 0.229
Thymus	6.637 \pm 1.861	4.206 \pm 2.722	0.809 \pm 0.531	0.285 \pm 0.232
Thyroids	10.299 \pm 3.153	6.492 \pm 3.183	1.323 \pm 0.668	<0.336 \pm 0.299
Uterus	16.010 \pm 3.477	10.134 \pm 5.652	2.137 \pm 1.610	0.655 \pm 0.528

^a Data were obtained from Tables 31-34 on pages 72-75 of MRID 51136001; n = 3 rats/time point.

The radioactive residues levels in all selected tissues and organs generally were less than the limits of quantification or detection by 168 h post-dose in either dose group (Groups B1 and D1). A table summarizing the radioactive residue levels at 168-h post-dose was shown on page 38 of MRID 51136001 and is included as Appendix V at the end of the DER.

Tissue concentrations of radioactive residues at 168 h post-dose at 0.5 mg/kg were at or less than the lower limits of quantification. Tissue concentrations of radioactive residues at 168 h post-dose at 200 mg/kg were quantifiable in the kidneys (0.02 and 0.03 $\mu\text{g-equiv/g}$), plasma (0.01 and 0.03 $\mu\text{g-equiv/g}$), liver (0.01 and 0.01 $\mu\text{g-equiv/g}$), and lungs (0.01 and 0.01 $\mu\text{g-equiv/g}$) in males and females, respectively, as well as the blood, muscle, pancreas, and spleen (0.01 $\mu\text{g-equiv/g}$) and uterus (0.02 $\mu\text{g-equiv/g}$) in females. All other tissue concentrations were at or less than the lower limits of quantification. Radioactive residues in the residual carcasses at 168 h post-dose were at or less than the lower limits of quantification in the 0.5 mg/kg dose group and 0.29 and 0.40 $\mu\text{g-equiv/g}$ in male and female rats, respectively, in the 200 mg/kg dose group.

III. DISCUSSION AND CONCLUSIONS

- A. INVESTIGATORS' CONCLUSIONS:** The orally-administered test substance was rapidly and almost completely absorbed from the gastrointestinal tract into the systemic circulation at both dose levels (*i.e.*, 0.5 and 200 mg SAN 837 H [dicamba]/kg body weight). The extent of absorption, based on the amount renally excreted and the remaining tissue residues, was at least 90% of the dose independent of the dose level and the sex.

The maximum concentration (C_{max}) estimates in blood at both dose levels and both sexes were reached within 0.5 h after administration accounting for about 0.1 $\mu\text{g-equiv/g}$ (ppm) and 60 $\mu\text{g-equiv/g}$ dicamba equivalents for the low- and high-dose level, respectively. A second maximum was observed between 2 and 4 h after administration at a somewhat lower

level (*i.e.*, about 0.06 µg-equiv/g at the low-dose level and 30 µg-equiv/g at the high-dose level). After reaching the second maximum, the residues in blood depleted within 3 to 6 h to half of the second maximum concentration in blood. The AUC_{0-48 h} values revealed a slight difference between both sexes (*i.e.*, 0.368 µg-equiv × h/g and 0.583 µg-equiv × h/g at the low-dose level and 273 µg-equiv × h/g and 315 µg-equiv × h/g at the high-dose level for males and females, respectively). Based on the calculated AUC_{0-48 h}, the females tended to a higher bioavailability as compared to males, more obvious at the low-dose level. The increase of the dose level (1:400) compared with the increase of the AUC values (1:740 for males and 1:540 for females) revealed a non-proportionality indicating a higher systemic bioavailability at the high-dose level.

Evidence was given for enterohepatic circulation based on the presence of a second maximum in the figure of blood kinetics and the slightly higher systemic bioavailability at the high-dose level even though the test substance was almost completely absorbed at both dose levels.

The oral administered doses were rapidly excreted. The predominant part of the dose was excreted with the urine (*i.e.*, more than 90% of the dose at both dose levels and both sexes). Only very small amounts were excreted with the feces, accounting for about 2%, essentially independent of sex and dose level. The amount of radioactivity exhaled was insignificant. The residues 7 days after oral administration were very low, not exceeding 0.2% of the applied dose for both dose levels and both sexes.

After absorption the test substance was widely distributed in the whole body of the animals. All selected tissues and organs showed their maximum residue values 4 h after administration at very low levels.

At the low-dose level (0.5 mg/kg), the highest residue values were found in kidneys at 0.20/0.33 µg-equiv/g of males/females, respectively. All other selected tissues and organs showed maximum residue levels at or below 0.05 µg-equiv/g, except plasma (0.07/0.15 µg-equiv/g) and uterus (0.06 µg-equiv/g). The maximum tissues residue levels in females tended to higher values (up to two times) as compared with males. The depletion half-lives ($t_{1/2}$) for the tissue residues were calculated to be in the range of 2 to 3 h for both sexes. The ultimately-determined tissue residues seven days after oral administration were all below the limit of determination.

The tissue distribution and depletion pattern after administration at the high dose level (200 mg/kg body weight) was very similar to that observed at the low-dose level. The maximum residue levels were about 250-450 times higher in correspondence with the increased dose level. Again, the kidneys showed the highest maximum levels. The calculated half-lives at the high-dose level were in the range of 2 to 4 h independent of the sex. As a consequence of the rapid depletion, the tissue residues seven days after administration were extremely low not exceeding 0.04 µg-equiv/g.

At both dose levels, only 3% of the administered dose was recovered in selected tissues and organs 4 h after administration at the low- and high-dose level. The tissue residues depleted

to totally 0.2% of the dose within 16 h after administration at both dose levels and independent of the sex.

- B. REVIEWER COMMENTS:** No unusual behavior was observed in any treatment group prior to or after dose administration. Some females in Groups B1 and D1 (2/4 per group) had body weight decreases of up to 4% during the seven-day post-dose period and approximately 50% of the rats in Groups F1-F4 had body weight decreases of up to 5% prior to euthanasia at up to 16 h post-dose. These minimal decreases were considered unrelated to treatment.

Mean blood concentrations at each time point were generally similar between males and females at each dose level although occasional differences of approximately ≤ 2 -fold occurred. Serial blood concentrations after administration of 0.5 mg/kg [^{14}C]-dicamba to male and female rats were quantifiable through 8 h and 12 h post-dose, respectively, and concentrations after administration of 200 mg/kg [^{14}C]-dicamba were quantifiable through 48 h post-dose in both sexes.

After administration of 0.5 mg/kg [^{14}C]-dicamba to male and female rats, the C_{max} of radioactive residues in whole blood was 0.11 and 0.13 $\mu\text{g-equiv/g}$, respectively, at 0.5 h (T_{Cmax1}). A second maximum in males and females of 0.05 and 0.08 $\mu\text{g-equiv/g}$, respectively, was reached at 2 and 4 h (T_{Cmax2}) and blood concentrations declined from the secondary peaks by half within 3-5 h (7 h post-dose). After administration at 200 mg/kg to male and female rats, the C_{max} of radioactive residues in whole blood was 67.6 and 50.5 $\mu\text{g-equiv/g}$, respectively, at 0.5 h (T_{Cmax1}). A second maximum in males and females of 32.9 and 30.7 $\mu\text{g-equiv/g}$, respectively, also was reached at 4 h (T_{Cmax2}) and blood concentrations declined from the secondary peaks by half within 3-6 h (7-10 h post-dose).

Estimates of AUC_{0-t} in the 0.5 mg/kg males and females were 0.37 and 0.58 $\mu\text{g-equiv} \times \text{h/g}$, respectively. Estimates of AUC_{0-t} in the 200 mg/kg males and females were 273 and 315 $\mu\text{g-equiv} \times \text{h/g}$, respectively. Estimates of AUC_{0-t} for females were greater compared to males and this difference was more evident after administration of 0.5 mg/kg with an increase of approximately 60% in females compared to males. At the high dose, the estimated AUC_{0-t} values increased in both sexes in a non-proportional manner with increases of approximately 742-fold for males and 541-fold for females for the 400-fold dose ratio.

Oral administration of [^{14}C]-dicamba at 0.5 or 200 mg/kg resulted in nearly complete absorption from the gastrointestinal tract into the systemic circulation. Estimated oral bioavailability was generally $>90\%$ of the administered dose independent of dose level and sex. The percentages and rates of excretion in urine and feces through 168 h generally were similar between males and females and regardless of dose level. Recovery of radioactive residues in urine was rapid with $>95\%$ and approximately 85% excreted in males and females, respectively, at 0.5 mg/kg and $>95\%$ excreted in both sexes at 200 mg/kg. Recovery of radioactive residues in feces was minor with approximately 1-2% of the administered dose recovered. Less than 0.01% of the administered radioactivity was detected in the expired-air traps through 48 h post-dose in the 200 mg/kg dose group.

Similarly, recoveries of radioactive residues in excise tissues/organs at 168 h post-dose were <0.1% of the administered doses. The percentage of radioactive residues remaining in the residual carcasses at 168 h post-dose administration was <0.1% for the 0.5 mg/kg males and <0.2% for the 0.5 mg/kg females and the 200 mg/kg rats. Total recoveries after administration of the 0.5 mg/kg dose were approximately 92-99% with approximately 98-100% recovered after administration of the 200 mg/kg dose.

The radioactive residue levels in all selected tissues and organs were greatest at 4 h post-dose which generally corresponded to the second blood maximum concentration. The tissue elimination half-life estimates generally were 2 h for the 0.5 mg/kg treatment group and 2 or 3 h for the 200 mg/kg treatment group illustrating the rapid tissue clearance at both dose levels.

At 0.5 mg/kg, the greatest tissue concentrations in males and females were observed in kidneys (0.20 and 0.33 µg-equiv/g, respectively), with further concentrations of ≥ 0.05 µg-equiv/g in plasma and blood as well as the lungs, ovaries, and uterus in females. The maximum radioactive residue concentrations in all other tissues were <0.05 µg-equiv/g. Maximum tissue radioactive residue concentrations were up to 2-fold greater in females compared to males. Tissue concentrations were close to or less than the lower limits of quantification or detection within 16 h post-dose.

At 200 mg/kg, the greatest tissue concentrations in males and females were observed in kidneys (86.9 and 68.6 µg-equiv/g, respectively), plasma (34.9 and 39.6 µg-equiv/g, respectively), and blood (21.0 and 23.3 µg-equiv/g, respectively), with further concentrations between 10-20 µg-equiv/g in adrenals, heart, liver, and lungs as well as the thyroids, ovaries, and uterus in females. The maximum radioactive residue concentrations in all other tissues were <10.0 µg-equiv/g. Maximum tissues radioactive residue concentrations generally were similar in females compared to males. Tissue concentrations generally were greater than the limits of quantification through 16 h post-dose.

Tissue concentrations of radioactive residues at 168 h post-dose at 0.5 mg/kg were at or less than the lower limits of quantification. Tissue concentrations of radioactive residues at 168 h post-dose at 200 mg/kg were quantifiable (0.01-0.03 µg-equiv/g) in the kidneys, plasma, liver, and lungs in males and females as well as the blood, muscle, pancreas, spleen, and uterus in females. All other tissue concentrations were at or less than the lower limits of quantification. Radioactive residues in the residual carcasses at 168 h post-dose were at or less than the lower limits of quantification in the 0.5 mg/kg dose group and 0.3-0.4 µg-equiv/g in the 200 mg/kg dose group.

This study is classified **acceptable/guideline** and satisfies the guideline requirements for a metabolism study [OCSP 870.7485, OECD 417] in rats.

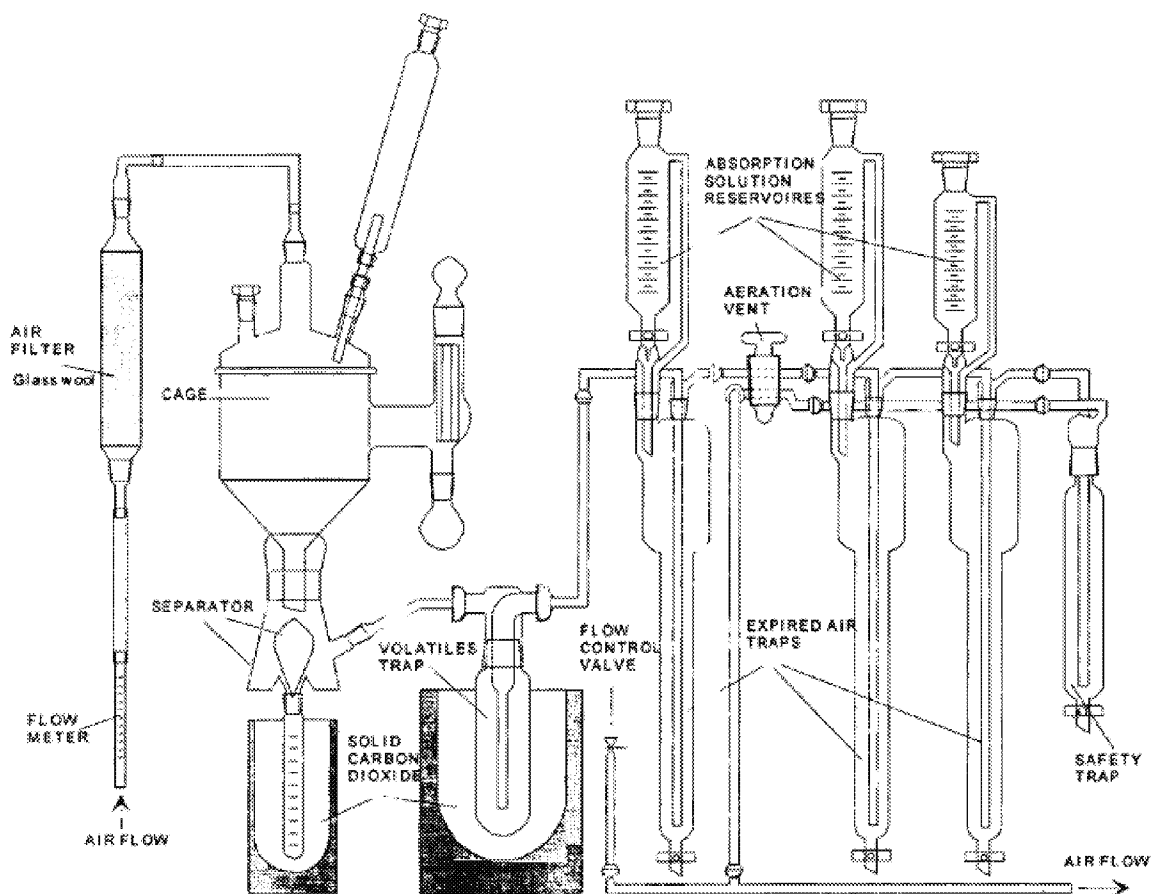
C. STUDY DEFICIENCIES: Minor study deficiencies were observed:

- Certificates of analysis for the radiolabeled and unlabeled test substances were not provided.
- Storage conditions for the radiolabeled and unlabeled test substances were not provided.

Appendix I. Thin-layer chromatography plates and solvent systems used for the determination of radiochemical stability of formulated [phenyl-U-¹⁴C]-dicamba.

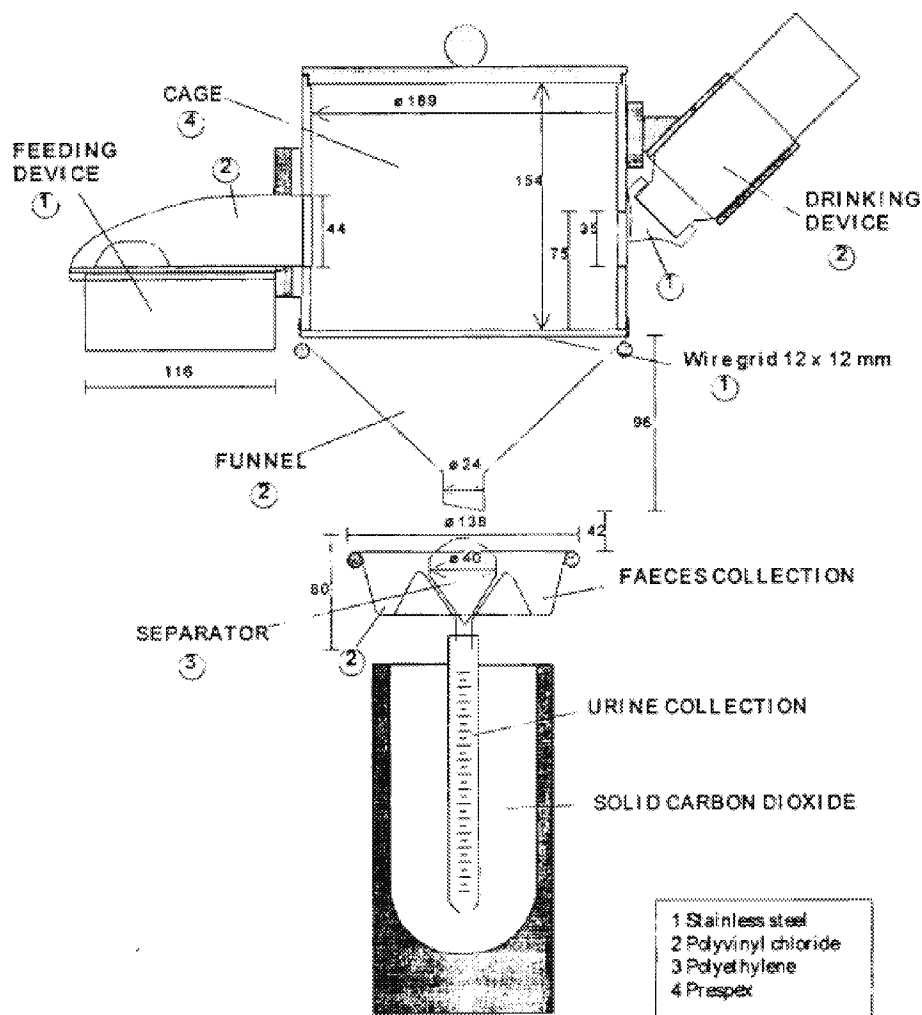
Plate: Silica gel SI 60 F₂₅₄ (without chamber saturation)
CI-1 toluene/acetone/acetic acid (65/35/5 v/v/v)
R_f (SAN 837 H): 0.6
Plate: Reversed phase RP 18 F₂₅₄ (without chamber saturation)
CI-2 acetonitrile/water (8/2 v/v)
R_f (SAN 837 H): 0.7

(copied from page 28 of MRID 51136001)

Appendix II. Closed all-glass metabolism cage system.

(copied from page 80 of MRID 51136001)

Appendix III. Open plexiglass metabolism cage system.



(copied from page 82 of MRID 51136001)

Appendix IV. Maximum radioactive residue amounts ($\mu\text{g-equiv/g}$) and tissue elimination half-life estimates after single oral gavage administration of [phenyl- ^{14}C]-dicamba to male and female rats at 0.5 or 200 mg/kg.

Maximum tissue residues [ppm SAN 837 H equivalents) and depletion half life								
Group	F1		F2		F3		F4	
Sex	males		females		males		females	
Dose level [mg/kg]	0.5		0.5		200		200	
	ppm	$t_{1/2}$ [h]	ppm	$t_{1/2}$ [h]	ppm	$t_{1/2}$ [h]	ppm	$t_{1/2}$ [h]
Adrenals	0.0188	3	0.0414	2	16.657	2	10.114	2
Blood	0.0453	2	0.0880	2	20.978	2	23.321	2
Bone	0.0120	2	0.0143	2	4.871	3	3.566	4
Brain	0.0023	n.a.	0.0039	2	1.085	2	1.366	3
Fat	0.0050	2	0.0090	2	1.875	3	1.841	3
Heart	0.0291	2	0.0395	2	13.116	2	15.399	2
Kidneys	0.2003	2	0.3288	2	86.880	3	68.568	3
Liver	0.0372	2	0.0396	2	12.219	3	14.217	2
Lungs	0.0314	2	0.0602	2	14.653	2	17.620	2
Muscle	0.0136	2	0.0212	2	5.661	2	5.701	2
Ovaries	n.a.	n.a.	0.0527	2	n.a.	n.a.	13.112	3
Pancreas	0.0211	2	0.0369	3	7.018	4	9.165	2
Plasma	0.0748	2	0.1491	2	34.945	2	39.567	2
Spleen	0.0180	2	0.0198	2	6.901	3	7.749	2
Testes	0.0193	2	n.a.	n.a.	5.675	3	n.a.	n.a.
Thymus	0.0119	2	0.0210	2	4.899	2	6.637	2
Thyroids	0.0196	n.a.	0.0291	n.a.	7.431	2	10.299	3
Uterus	n.a.	n.a.	0.0608	2	n.a.	n.a.	16.010	2

n.a. not applicable

(copied from page 35 of MRID 51136001)

Appendix V. Radioactive residue amounts ($\mu\text{g-equiv/g}$) at 168 h post-dose after single oral gavage administration of [phenyl- ^{14}C]-dicamba to male and female rats at 0.5 or 200 mg/kg.

Tissue residues 7 days after a single oral administration [ppm SAN 837 H equivalents]						
Group	B1			D1		
Sex	male	female	LQ	male	female	LQ
Dose	0.53	0.55		199.1	201.3	
Adrenals	< LQ	< LQ	0.0020	< LD	= LD	0.026
Blood	< LD	< LD	0.0009	< LQ	0.011	0.008
Bone	< LD	< LD	0.0008	< LQ	< LQ	0.009
Brain	< LD	< LD	0.0007	< LD	= LD	0.007
Fat	< LD	< LD	0.0007	< LQ	< LQ	0.007
Heart	< LD	< LD	0.0008	< LQ	= LQ	0.008
Kidneys	< LD	= LD	0.0007	0.020	0.034	0.008
Liver	= LD	= LD	0.0007	0.009	0.013	0.007
Lungs	< LD	< LD	0.0009	0.008	0.009	0.008
Muscle	< LD	< LD	0.0007	< LQ	0.010	0.007
Ovaries	n.a.	< LD	0.0042	n.a.	< LD	0.044
Pancreas	< LD	< LD	0.0015	< LD	0.014	0.013
Plasma	< LD	< LD	0.0005	0.011	0.025	0.006
Spleen	< LQ	< LQ	0.0009	< LQ	0.012	0.011
Testes	< LD	n.a.	0.0006	< LQ	n.a.	0.006
Thymus	< LD	< LD	0.0009	< LQ	< LQ	0.009
Thyroids	< LQ	< LQ	0.0084	< LD	< LD	0.120
Uterus	n.a.	< LD	0.0013	n.a.	0.016	0.015
Carcass	< LD	0.0010	0.0009	0.294	0.401	0.008

(copied from page 38 of MRID 51136001)